

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 4 of 11

matter in a continuation application or to take other such appropriate measures to protect the inventions encompassed by this canceled subject matter.

The specification has been amended at page 11, line 10, to remove a hyperlink. The abstract has been amended to comprise only one paragraph, as is required (MPEP §608.01(b)).

Claims 1-2, 5-17, and 19-29 are now pending in the application. The Examiner's comments in the Office Action are addressed below in the order set forth therein.

The Objections to the Specification Should Be Withdrawn

The Office Action has objected to the specification under MPEP §608.01 for containing embedded hyperlinks and/or other forms of browser-executable code. In response, Applicant notes that MPEP §608.01 specifically defines a hyperlink or a browser-executable code as "a URL placed between these symbols '<>'" and "http://" followed by a URL address." From this language it is clear that it is not a URL which is itself objectionable, only the hyperlink that results from the enclosure of a URL within the "<>" pair or after the "http://" character string, an interpretation which is consistent with the policy goal of preventing live web links in documents on the USPTO web page that might direct a user to a commercial site over which the USPTO has no control, rather than any policy against URLs *per se*. See MPEP §608.01.

In light of the above discussion, Applicant has amended the specification at page 11, line 10, to remove the "www" at the beginning of the website address, thereby removing the hyperlink and/or browser-executable code. The URL now contained in the specification is consequently not a live weblink such as a hyperlink or browser-executable code. Because this URL is not a hyperlink or browser-executable code as defined in MPEP §608.01, the objection should be withdrawn.

The abstract of the disclosure has been objected to because it comprises two paragraphs. The abstract has been corrected to comprise only one paragraph, and, therefore, the objection should be withdrawn.

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 5 of 11

The Objection to the Claims Should Be Withdrawn

Claims 1, 6, and 16 are objected to because they recite non-elected species. These claims have been amended to remove the non-elected species. Therefore, the objection should be withdrawn.

Upon the allowance of a generic claim (i.e., claim 1 or claim 16), Applicant expressly reserves the right to request consideration of claims to additional species of FGF-2, which would be written in dependent form or would otherwise include all of the limitations of the allowed generic claim as provided by 37 C.F.R. §1.141.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Claims 1-29 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to use the invention. This rejection is respectfully traversed.

The Office Action states that "the specification does not provide any guidance of how to use FGF to treat or prevent erectile dysfunction, because it does not disclose one single case where erectile dysfunction is treated or prevented using FGF" and that the claims are not enabled because the "specification does not present any data showing that the administration of FGF does treat or prevent erectile dysfunction" (Office Action mailed November 18, 2002, at pages 3 and 4, item 4a). As an initial matter, Applicant respectfully submits that in fact there is no *per se* requirement of 35 U.S.C. §112, first paragraph, enablement, that any particular sort of data such as experimental data be provided. Instead, the requirement for adequate enablement is simply one of experimentation that is not undue. Thus, as stated in the *Manual of Patent Examining Procedure* (MPEP) §2164.01, "[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation" (quoting *United States v. Telectronics, Inc.*, 857-F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988)).

The presently claimed invention is based on anecdotal observations during a phase I clinical trial investigating the use of FGF-2 to treat coronary artery disease. In this trial, patients received a single intraarterial infusion of recombinant FGF-2 at doses in the range provided in Applicant's specification. During the course of this clinical trial, some of the patients receiving

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 6 of 11

the FGF treatment volunteered that their sexual activities were more satisfactory as a result of improved erectile function. Thus, the efficacy of the presently claimed invention has already been demonstrated by Applicant using the methods disclosed in the present specification. As such, Applicant respectfully submits that the specification is enabling for one skilled in the art to use the presently claimed invention.

Further, Applicant has disclosed the therapeutically effective doses of FGF to be administered and has taught the method of administering these doses of FGF. See the specification, for example, at pages 4-6. Applicant submits that one of skill in the art can readily practice the claimed invention having been apprised of the disclosure set forth in the present specification, and can further assess the efficacy of the claimed methods, all of which can be carried out without undue experimentation. In this manner, one need administer FGF at the recommended dosage, in accordance with a recommended route of administration, and assess the desired therapeutic response, i.e., an objective improvement in erectile function in the patient, by measuring the ability of the patient to achieve and sustain an erection. See the specification, for example, at page 6.

In view of these remarks, Applicant respectfully submits that the specification is enabling for the claimed invention. Accordingly, this rejection of the claims should be withdrawn.

Claims 6-14 and 21-29 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor had possession of the claimed invention at the time the application was filed. This rejection is respectfully traversed.

The claims are drawn to a method for treating or preventing erectile dysfunction, or a method for improving erectile function, where the method comprises administering a therapeutically effective amount of a biologically active fragment or mutein of the FGF of SEQ ID NO:2 or 4. The Office Action notes that "the structure of biologically active fragments or muteins are not defined" (Office Action mailed November 18, 2003, at page 5, item 4b). However, the definition of an angiogenically or biologically active fragment of FGF-2 (applying to both SEQ ID NO:2 and 4), as found on page 17, lines 19-26, states that the fragment "has about 80% of the 146 residues of SEQ ID NO:2" and "retains the angiogenic or biological effect

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 7 of 11

of the FGF-2 of SEQ ID NO:2." This definition includes both structure (having 80% of the residues of SEQ ID NO:2 or 4) and function (retaining angiogenic or biological effect of SEQ ID NO:2 or 4).

The Office Action further states that the written description only discloses the FGF of SEQ ID NO:2 and 4, and therefore is not commensurate in scope with the claims drawn to a method for treating, improving, or preventing erectile dysfunction, comprising administering a therapeutically effective amount of a biologically active fragment or mutein of SEQ ID NO:2 or 4. However, on page 14, lines 22-24, angiogenically active muteins of FGF-2 are disclosed, as those described in U.S. Patent Nos. 5,859,208 and 5,852,177, both of which are incorporated by reference. In addition, several biologically active fragments of FGF-2 that have N-terminal truncations are disclosed on page 18, lines 19-25 (as disclosed in U.S. Patent No. 5,155,214), as well as the biologically active fragments disclosed in U.S. Patent No. 5,155,214 (page 18, lines 26-29). The specification states "the biologically active fragments of a mammalian FGF typically encompass those terminally truncated fragments of an FGF-2 that have at least residues that correspond to residues 30-110 of rFGF-2 of SEQ ID NO:2; more typically, at least residues that correspond to residues 18-146 of rFGF-2 of SEQ ID NO:2." The requirement that the synthetic peptides and hybrid FGF molecules will retain the ability to bind with FGF receptors is also included. Thus, numerous biologically active muteins and fragments of FGF-2 are disclosed in the specification, not merely SEQ ID NO:2 and 4.

Furthermore, the specification provides guidance as to which areas of FGF-2 are important for cellular and heparin binding, and notes that fragments preferably retain both cell binding sites and at least one heparin binding site. See page 18, lines 28-29. General guidance as to conservative substitutions to be made to generate FGF muteins is provided (see page 19, line 18, continuing through page 20, line 7). Examples of these conservative substitutions are disclosed, such as the substitution of serine for one or both of the cysteines at residue positions 87 and 92 of SEQ ID NO:2 or SEQ ID NO:4 (see page 19, lines 26-27). Methods for introducing point mutations are also disclosed (see page 20, lines 8-18).

Thus, Applicant respectfully submits that the specification discloses a representative number of different sequences that retain biological activity and that could be used in the methods of the invention, and also provides structural criteria that explicitly enable such

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 8 of 11

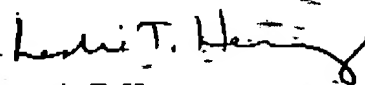
biological activity. Therefore, one skilled in the art would recognize that the inventor was in possession of the claimed invention and would have the ability to produce such a mutein or fragment. Accordingly, this rejection of the claims should be withdrawn.

### CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully submits that the objections to the specification and claims, and the rejection of the claims under 35 U.S.C. §112, first paragraph, are now overcome, and this application is now in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the Examiner, a telephone interview would expedite the prosecution of this application, the Examiner is invited to call the undersigned.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

  
Leslie T. Henry  
Registration No. 45,714

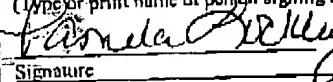
CUSTOMER NO. 00826  
ALSTON & BIRD LLP  
Bank of America Plaza  
101 South Tryon Street, Suite 4000  
Charlotte, NC 28280-4000  
Tel Raleigh Office (919) 862-2200  
Fax Raleigh Office (919) 862-2260

#### CERTIFICATION OF FACSIMILE TRANSMISSION

I hereby certify that this paper is being facsimile transmitted to  
Commissioner for Patents, Patent and Trademark Office at Fax No.  
703-872-9306 on the date shown below.

Pamela Lockley

(Type or print name of person signing certification.)

  
Signature

February 18, 2003  
Date

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 9 of 11

**Version with Markings to Show Changes Made:**

**In the Specification:**

Please amend the paragraph beginning on page 10, line 19, to read as follows:

Thus, the determination of percent identity between any two sequences can be accomplished using a mathematical algorithm. One preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller (1988) *CABIOS* 4:11-17. Such an algorithm is utilized in the ALIGN program (version 2.0), which is part of the GCG sequence alignment software package. A PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used with the ALIGN program when comparing amino acid sequences. Another preferred, nonlimiting example of a mathematical algorithm for use in comparing two sequences is the algorithm of Karlin and Altschul (1990) *Proc. Natl. Acad. Sci. USA* 87:2264, modified as in Karlin and Altschul (1993) *Proc. Natl. Acad. Sci. USA* 90:5873-5877. Such an algorithm is incorporated into the NBLAST and XBLAST programs of Altschul *et al.* (1990) *J. Mol. Biol.* 215:403. BLAST nucleotide searches can be performed with the NBLAST program, score = 100, wordlength = 12, to obtain nucleotide sequences homologous to a nucleotide sequence encoding the polypeptide of interest. BLAST protein searches can be performed with the XBLAST program, score = 50, wordlength = 3, to obtain amino acid sequences homologous to the polypeptide of interest. To obtain gapped alignments for comparison purposes, Gapped BLAST can be utilized as described in Altschul *et al.* (1997) *Nucleic Acids Res.* 25:3389. Alternatively, PSI-Blast can be used to perform an iterated search that detects distant relationships between molecules. See Altschul *et al.* (1997) *supra*. When utilizing BLAST, Gapped BLAST, and PSI-Blast programs, the default parameters of the respective programs (e.g., XBLAST and NBLAST) can be used. See the website at [\[www.ncbi.nlm.nih.gov\]](http://www.ncbi.nlm.nih.gov)[ncbi.nlm.nih.gov](http://ncbi.nlm.nih.gov). Also see the ALIGN program (Dayhoff (1978) in *Atlas of Protein Sequence and Structure* 5:Suppl. 3 (National Biomedical Research Foundation, Washington, D.C.) and programs in the Wisconsin Sequence Analysis Package, Version 8 (available from Genetics Computer Group, Madison, Wisconsin), for example, the GAP program, where default parameters of the programs are utilized.

Please amend the abstract, to read as follows:

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 10 of 11

Compositions and methods for improving erectile function in a patient are provided. Compositions comprise one or more angiogenic agents or growth factors. Such agents or growth factors are administered in therapeutically effective amounts to treat or prevent erectile dysfunction. Pharmaceutical compositions comprising a therapeutically effective amount of at least one angiogenic agent or growth factor and a pharmaceutically acceptable carrier are also provided. The methods of the invention to improve erectile function and treat erectile dysfunction comprise administering at least a single unit dose of a pharmaceutical composition comprising the angiogenic agent or growth factor, generally at a local target site in the patient. It is recognized that increased benefits may result from multiple dosing, including intermittent dosing.

In the Claims:

Please cancel claims 3 and 48.

Please amend claims 1, 4, 6, 16, 19, and 21 to read as follows:

1. (amended) A method for treating or preventing erectile dysfunction in a patient, said method comprising administering to said patient a therapeutically effective amount of a growth factor, wherein said growth factor is [selected from the group consisting of FGF, EGF, PDGF, VEGF, and TGF] fibroblast growth factor (FGF).

4. (amended) The method of claim [3]2, wherein said FGF is FGF-2.

6. (amended) The method of claim 5, wherein said FGF-2 comprises the sequence set forth in SEQ ID NO:2, SEQ ID NO:4, [SEQ ID NO:6, SEQ ID NO:8,] or a biologically active fragment or mutein thereof.

16. (amended) A method for improving erectile function in a mammal, said method comprising delivering at a target site in said mammal in a therapeutically effective amount a pharmaceutical composition, said composition comprising [a growth factor selected from the

In re: Whitehouse  
Appl. No.: 09/802,365  
Filed: March 9, 2001  
Page 11 of 11

group consisting of FGF, EGF, PDGF, VEGF, and TGF] fibroblast growth factor (FGF) and a pharmaceutically acceptable carrier.

19. (amended) The method of claim [18]17, wherein said FGF is FGF-2.

21. (amended) The method of claim 19, wherein said FGF-2 comprises the sequence set forth in SEQ ID NO:2, SEQ ID NO:4, [ SEQ ID NO:6, SEQ ID NO:8,] or a biologically active fragment or mutein thereof.

RTA01/2129851v1